

RESPONSE UNDER 37 C.F.R. § 1.114(c)
U.S. Application No. 10/590,311 (Q108487)

REMARKS

Status of Claims

Claims 1, 3-12, 14-17, 19-23 and 26-17 are all the claims pending in the application.

Response To Advisory Action

In the Advisory Action, the Office Action indicates that the Amendment under 37 C.F.R. § 1.116, filed January 27, 2009, was not entered because the amendments to the claims raise new issues that would require further search and/or consideration as:

- (a) new claims 26-27 are drawn to prophylaxis, which is asserted to have enablement issues; and
- (b) the amended claims are not deemed to place the application in form for appeal by materially reducing or simplifying the issues with regard to the rejection of claims 1-17 and 19-25 under 35 U.S.C. § 103.

Specifically, the Office Action appears to assert that Applicants' arguments that (1) Komai does not teach the effect of gellan sulfate on the IL-1 mediated degradation of cartilage as disclosed in Hill and the treatment of osteoarthritis, (2) osteoarthritis and rheumatoid arthritis are two different illnesses, (3) Hill does not exemplify treatment of osteoarthritis and does not teach treatment via oral administration, are not persuasive.

The Office Action asserts that because Hill teaches that polysulfated polysaccharides may be used to treat arthritis, these compounds may be used to treat osteoarthritis via direct injection into the synovial cavity of an arthritic joint. The Office Action appears to assert that although Hill does not teach or suggest oral administration, such oral administration would have been obvious because it is well known to one of ordinary skill in the art.

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Komai again appears to be asserted to teach a connection between gellan sulfate and rheumatoid arthritis. The Office Action states that both osteoarthritis and rheumatoid arthritis are defined in Dictionary.com and the Martindale and Osteoarthritis and Cartilage (1999) to involve degradation of bone joints, synovial inflammation and cartilage erosion/destruction. Thus, the Office Action asserts that since Hill teaches the use of polysulfated polysaccharides for osteoarthritis, and both rheumatoid and osteoarthritis involve degradation of bone joints, synovial inflammation and cartilage erosion/destruction, it would have been obvious for one of ordinary skill in the art to treat osteoarthritis as claimed using a polysulfated polysaccharides such as gellan sulfate.

The Office Action asserts that the Declaration of Ana Maria Gibert shows that a higher dosage (80 mg/Kg) of inulin polysulfate provides significant improvement. However, the Office Action appears to assert that such result is merely routine optimization of the dosage disclosed in Hill to obtain maximum beneficial effects using the same active agent, and would have been obvious to one of ordinary skill in the art.

The Office Action states that entry of the amendment would overcome the rejections under 35 U.S.C. § 112, first and second paragraphs.

The Advisory Action indicates that upon the filing of an appeal, the Amendment under 37 C.F.R. § 1.116, filed January 27, 2009, will not be entered and the status of the claims are claims 1-17 and 19-25 are rejected.

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Initially, Applicants note that the Office Action has failed to establish a *prima facie* case of obviousness based upon the erroneous reliance on the different definitions of osteoarthritis and rheumatoid arthritis to connect the disclosures in Hill and Komai.

First, the Office Action has ignored the well-established differences between osteoarthritis and rheumatoid arthritis. Namely, that osteoarthritis is a degenerative joint disease while rheumatoid arthritis is an inflammatory disease which involves an immunological component because the majority of patients with rheumatoid arthritis have increased rheumatoid factors with serum antibodies directed against immunoglobulin G (IgG). (See page 11, 2nd column, 1st paragraph under “Osteoarthritis” and 3rd column, 1st and 2nd paragraphs under “Rheumatoid arthritis” in Martindale - The Extra Pharmacopoeia). Although there may be synovial inflammation observed with advanced osteoarthritis, it is well recognized in the art that such inflammation is different in nature to that observed with rheumatoid arthritis. (See page 11, 2nd column, 1st paragraph under “Osteoarthritis” in Martindale - The Extra Pharmacopoeia).

Second, when the prior art teaches away from the claimed solution, the Board of Patent Appeals and Interferences noted that obviousness cannot be proven merely by showing that a known element could have been modified by routine experimentation or solely on the expectation of success. *Ex parte Whalen* (BPAI 2008).¹ “[I]t must be shown that those of

¹ The Supreme Court stated that “because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement...Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-1741 (2007).

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ordinary skill in the art would have had some apparent reason to modify the [art] in a way that would result in the claimed [invention].” Id.

In the present case, Hill teaches away from (1) using sulphated polysaccharides because such compounds would not “have the utility found by the present inventors [of Hill]” (see column 10, lines 38-53 of Hill), and (2) using polysulphated polysaccharides in the form of “pharmaceutically acceptable salts such as potassium and sodium” (see column 10, lines 47-49 of Hill). Instead, Hill discloses the use of metallic complexes of polysulphated polysaccharides because the “inventors [of Hill] found that when the polysulphated polysaccharides are present as particular complexes, the suppression of blood clotting mechanisms by the polysulphated polysaccharides is greatly reduced whilst the anti-arthritis, anti-inflammatory activity is enhanced.” (See column 9, lines 42-51 of Hill). In this regard, Hill explicitly discloses that “because of the unusually strong affinity of the metal in these complexes...for certain sulphate esters and oxygen atoms present on the carbohydrate rings of the polysaccharide, the metal alters the conformation and rigidity of the polymer chain thereby influencing its biological activity.” (See column 10, lines 54-60 of Hill). Accordingly, Hill explicitly *teaches away* from the presently claimed invention.

Further, as admitted by the Office Action, Hill does not teach the treatment of osteoarthritis using the claimed polysulphated polysaccharides. (see page 8, lines 1-2 of Office Action mailed October 27, 2008). Specifically, the polysulphated polysaccharides of Hill are stated to be “selected from the group consisting of dextran, xylan, chondroitin, dermatan and

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hyaluronic acid.”² (See column 9, lines 51-54 of Hill). Also, neither Hill nor Komai teach or suggest oral administration.

Further, pursuant to M.P.E.P. § 2144.08, to establish a *prima facie* case of obviousness, “it is essential that Office personnel find some motivation or suggestion to make the claimed invention *in light of the prior art teachings* [emphasis added].” In the present case, Komai is merely cited by the Office Action to teach a connection between gellan sulfate and rheumatoid arthritis. However, because Hill explicitly discloses the use of metallo complexes of polysulphated polysaccharides *instead* of polysulphated polysaccharides or a pharmaceutically acceptable salt of polysulphated polysaccharides, Hill *teaches away* from modifying its teachings with the gellan sulphate of Komai. In fact, based upon the disclosure in Hill, one of ordinary skill in the art would have been *discouraged* from modifying the teachings of Hill with the teachings of Komai.

Thus, based upon the disclosures in Hill and Komai, and the well-established differences between osteoarthritis and rheumatoid arthritis, one of ordinary skill in the art would have had *absolutely no* motivation or suggestion to combine, and to modify the teachings of Hill with those of Komai.

Fourth, the Office Action’s contention that it would have been obvious for one of ordinary skill in the art to orally administer the higher dose of inulin polysulphate described in the Declaration filed January 27, 2009, because such dose would have been obtained through

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routine optimization a dose disclosed in Hill, is erroneous. In this regard, Applicants note that there are no specific dosage ranges encompassed by the presently claimed method.

Further, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). In this regard, the Office Action has failed to point to the specific “dose” referred to in Hill to support this contention. Also, the µg/ml unit doses disclosed in Hill are based upon *in vitro* treatment of cells in tissue culture which is in complete contrast to the *in vivo* assay described in the Declaration that provides a dose based on an individual’s body weight (mg/kg). In addition, although Hill discloses doses for intra-articular administration of hydrocortisone and pentosan polysulphate (see column 8, lines 28-45 and Table 1 of Hill), such doses are based upon intra-articular injection to a rabbit, and are given in combination with a glucocorticoid to prevent the loss of proteoglycans from joints induced by weekly intra-articular administration of the polysulphated polysaccharides listed in Table 1 of Hill. (See column 8, lines 28-45 of Hill).

In addition, Hill does not teach or suggest an oral route of administration. Instead, Hill teaches the use of hyaluronic acid by an intra-articular route³ that is well established in the prior art, as explained for example, in Martindale which states that “[i]mprovements of symptoms has

³ Hills describes also the administration by intraarticular route: See “Disclosure of invention”, column 3, lines 16-25, where it is written “administering to an affected joint.”

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been obtained with intra-articular injections of sodium hyaluronate, hylan, or superoxide dismutases.”⁴ One of the polysaccharides selected by Hills is a derivate from hyaluronic acid.⁵

Thus, for at least the reasons previously presented and discussed above, one of ordinary skill in the art would have had *no* motivation to combine Hill and Komai to obtain the presently claimed invention based upon the disclosures of Hill and Komai. Also, even if one of ordinary skill in the art was somehow motivated to make such a combination, such a combination would not have resulted in the presently claimed invention.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

⁴ See page 11, 2nd column under “osteoarthritis”.

⁵ “The effective polysulphated polysaccharides are believed to be those polysaccharides selected from the group consisting of dextran, xylan, condroitin, dermatan and hyaluronic acid.” See column 9, lines 51-54 of Hill.

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Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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